Does the method of lung preservation influence outcome after transplantation? An analysis of 681 consecutive procedures

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Objective: Despite 50 years of lung preservation research, the optimal preservation technique is undefined. Using data from a national cohort, we investigated outcomes with different preservation methods after adult lung transplantation.

Methods: Early (30-day), late (30-day to 3-year), and overall (3-year) mortalities, adjusted for differences in donor and recipient characteristics, were compared by using Cox regression. Intensive care unit length of stay and the number of rejection episodes were secondary outcomes.

Results: Six hundred eighty-one eligible lung transplantations between July 1995 and June 2003 were preserved with Euro–Collins solution (n = 284), blood albumin (n = 139), core cooling (n = 107), or low potassium dextran solution (n = 151). There was significantly increased use of low potassium dextran solution over time ($P < .001$). Unadjusted 3-year survival was similar across the groups ($P = .72$), with the highest 3-year survival in the low potassium dextran group (62%; 95% confidence interval, 51%–72%) and the lowest in the blood albumin group (49%; 95% confidence interval, 39%–58%). Risk-adjusted early ($P = .70$), late ($P = .27$), and overall ($P = .72$) survival was similar across the groups and was not affected by ischemic time. Freedom from death caused by primary graft dysfunction was again highest in the low potassium dextran group (95%; 95% confidence interval, 90%–98%) and lowest in the blood albumin group (91%; 95% confidence interval, 85%–95%). There was no difference in intensive care unit length of stay. An increased incidence of rejection was apparent with increasing ischemic time ($P = .067$).

Conclusion: The methods of lung preservation in current use do not seem to affect early or midterm survival after transplantation, but increasing ischemic time might predispose to increased rejection.

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This study was carried out with the support of funding from the Department of Health, United Kingdom.

Received for publication Aug 10, 2006; revisions received March 9, 2007; accepted for publication May 11, 2007.

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J Thorac Cardiovasc Surg 2007;134:1313-21

0022-5223/$32.00

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doi:10.1016/j.jtcvs.2007.05.030

The early and longer-term success of lung transplantation (LTx) is confounded by a high incidence of early and late graft failure. Five-year survival rates approximate 50% or less.[1] Primary graft failure is the predominant cause of death (30%) within 30 days, whereas late graft failure caused by bronchiolitis obliterans syndrome (BOS) is the main cause of survival attrition after the first year.[1] The quality of lung preservation might be a key determinant of both early[2] and late[3] graft function.

Abbreviations and Acronyms

BA = blood albumin
BOS = bronchiolitis obliterans syndrome
CC = core cooling
CI = confidence interval
dPGD = death caused by primary graft dysfunction
EC = Euro–Collins
IQR = interquartile range
LPD = low potassium dextran
LTx = lung transplantation
PGD = primary graft dysfunction
UKCTA = United Kingdom Cardiothoracic Transplant Audit

Within 5 years of the clinical introduction of heart–lung transplantation, distant procurement became possible. Lung ischemic protection was afforded mainly by hypothermia. This was induced either by surface cooling of the collapsed lung, core cooling (CC) on cardiopulmonary bypass, or flush perfusion with a variety of intracellular- or extracellular-type perfusates. Modified Euro–Collins (EC) solution flush, administered at 15 mL · kg^{-1} · min^{-1} for a total volume of 60 mL · kg^{-1}, became the most commonly used perfusate, whereas others adopted blood albumin (BA)–based preservation fluids and CC. Despite these techniques, increasing early mortality with increasing ischemic time was identified, and much subsequent experimental work led to the development of low potassium dextran (LPD) solution as a potentially improved method of preservation.[3-7] However, comparison of outcomes with LPD solution versus other conventional preservation techniques in the literature reveals varying results.[7-10] Despite 5 decades of clinical and laboratory research evaluating methods of lung preservation,[11-13] there have been few studies examining the effect of preservation technique on survival after LTx. To identify differences, if any, in outcomes with current lung preservation techniques, we analyzed data from the United Kingdom Cardiothoracic Transplant Audit (UKCTA).

Materials and Methods

The UKCTA is a national cohort study. Data on all lung transplantation procedures in the United Kingdom have been collected since April 1995. Information is accrued prospectively at registration on the national waiting list, at the time of transplantation, and at regular intervals (90 days and annually) thereafter. Follow-up data on survival are 100% complete, and the accuracy and consistency of the data is maintained by means of regular computer-based and case record validation. Criteria for donor acceptance in the United Kingdom have been described previously.[14]

In this study we analyzed first-time isolated lung transplantations in adults (≥16 years) between July 1995 and June 2003 using lungs from cadaveric donors. Heart-lung transplantations were excluded. Thirty-day, 1-year, and 3-year survivals were the primary end points of the study. Length of stay in the intensive care unit and numbers of rejection episodes were secondary outcomes. A further secondary end point was death caused by primary graft dysfunction (dPGD). This was defined as the presence of 1 of the following factors: pulmonary infiltrates in the transplanted lung or lungs (bilateral in bilateral sequential lung transplant) on chest radiography with a pulmonary capillary wedge pressure of less than 18 cm H_2O, Pao_2/fraction of inspired oxygen ratio of less than 300 in the first 24 hours, or recipient ventilation for longer than 5 days because of respiratory compromise (not associated with atelectasis or infection). Cases were excluded if death was due to technical problems during surgical intervention or if there was evidence of acute or hyperacute rejection. Primary graft dysfunction (PGD) might predispose to infective complications or secondary organ failure, and death certificate coding might fail to attribute death to the primary causative factor of PGD. In view of this, case records for all in-hospital deaths after LTx between July 1995 and December 2002 were reviewed, and dPGD was validated by 3 independent analysts according to the predetermined criteria.

Ischemic time was defined as the time from donor crossclamping to reperfusion with recipient blood. For double-lung transplantations, when 2 times were reported, the earliest reperfusion time was used because these transplantations would have been done without cardiopulmonary bypass. A rejection episode was defined as a clinical event usually but not always accompanied by an abnormal transbronchial biopsy result that resulted in augmentation of the patient's immunosuppression. Histologic features of mild rejection that did not lead to a change in the immunosuppressive regimen and increases in immunosuppression to maintain blood levels or other therapeutic goals were not counted.

Lung perfusion techniques were classified into 4 categories: EC solution,[15,16] BA,[17,18] CC,[19-21] or LPD solution.[22,23] Vasodilator prostaglandins (prostacyclin or prostaglandin E_1) were used as an adjunct for all antegrade pulmonary artery flush techniques but not CC. Data on other vasodilators, including systemic nitric oxide donors, were not available.

Donor and pretransplantation recipient characteristics were compared by using the χ^2 or Fisher exact tests (categoric data) or the Kruskal–Wallis test (continuous data). The Fisher exact test was chosen when greater than 20% of the expected frequencies were less than 5.

Survival estimates, including freedom from dPGD during the admission for transplantation, were derived by using the Kaplan–Meier method, and survivals across the lung perfusion groups were compared by using the log–rank test. Cox proportional hazards regression[24] was used to examine the effect of preservation method on survival, after adjusting for potentially confounding factors. A clinical review of the database was undertaken to identify the potentially important variables to include. The effect of the chosen factors, together with the preservation method, was evaluated for the 3 epochs: early (≤30 days), late (30 days to 3 years), and overall (3 years) survival. These time periods were chosen to reflect the times when patients experience early and late graft failure/dysfunction. The differential effect of lung perfusion method on survival for transplantations with short (<210 minutes), medium (211–270 minutes and 270–330 minutes), and long (>330 minutes) ischemic times was investigated through the inclusion of interaction terms. Transplantation center was accommodated in 2 ways: (1) by including center as a covariate and (2) by

Table 1. Donor characteristics

	Euro–Collins solution (n = 284)	Blood albumin (n = 139)	Core cooling (n = 107)	Low potassium dextran solution (n = 151)	*P* value
Age (y)	35 (23–46)	40 (31–51)	41 (29–51)	37 (23–48)	<.001
Female sex (n)	128 (45%)	71 (51%)	48 (45%)	70 (46%)	.7
CMV positive (n)*	138 (49%)	66 (48%)	45 (45%)	67 (45%)	.8
Body mass index	22.7 (20.8–24.5)	23.1 (21.4–24.7)	23.4 (21.8–26.1)	23.7 (21.6–26.0)	.01
Inotropic use (n)	52 (19%)	35 (27%)	14 (14%)	45 (39%)	<.001

CMV, Cytomegalovirus. *Less than 5% missing data.

stratification. The proportional hazards assumption was examined for each model fitted. Results are presented as hazard ratios with 95% confidence intervals (CIs).

Freedom from dPGD was estimated by using the competing risks method, and survival across the lung preservation groups was compared by using the log–rank test. Length of intensive care unit stay was compared by using the log–rank test, and negative binomial regression[25] was used to compare posttransplantation rejection rates to 3 years across the groups after adjusting for follow-up time and potential confounding factors (diagnosis, transplant type, cytomegalovirus [CMV]–positive organ given to a CMV-negative recipient, blood group compatibility, ischemic time, audit year, and transplantation center). Again, the differential effect of lung perfusion method on rejection rates for transplantations with short, medium, and long ischemic times was investigated through the inclusion of interaction terms. Time to first rejection episode, adjusting for the same potential confounding factors, was compared by using Cox proportional hazards regression stratified by center.

All analyses were carried out with STATA software (release 8.2; Stata Corp, College Station, Tex).

Results

We analyzed 681 primary isolated lung (345 single and 336 bilateral) transplantations. EC solution was used as the preservation technique in 284 (42%), BA in 139 (20%), CC in 107 (16%), and LPD solution in 151 (22%) transplantations.

Donor characteristics are reported in Table 1. Donor age, body mass index, and need for inotropes differed between groups ($P \leq .01$). Lungs preserved in EC and LPD solutions were from younger donors than lungs preserved with BA and CC, and lungs preserved with EC solution were from donors with a lower median body mass index compared with those in the other groups. The need for inotropes was greatest in the LPD group (39%), whereas in the EC and CC groups, fewer than 20% of donors required inotropes.

Pretransplantation recipient characteristics are detailed in Table 2. Recipients of BA-perfused lungs had the highest median age (53 vs 51 years or lower in other groups) and were more likely to be taking prednisolone (56%) compared with recipients of other lungs. Recipients of LPD-preserved lungs had the lowest rate of pretransplantation steroid use (36%), whereas in the EC and CC groups 48% and 49% of patients were taking prednisolone, respectively ($P = .008$). The distribution by diagnosis differed between the groups; emphysema was the most prevalent diagnosis in all groups, followed by pulmonary fibrosis in the EC, BA, and CC groups and cystic fibrosis in the LPD group. Few en bloc double-lung transplantations were carried out; in the EC group the majority of transplantations were single-lung transplantations, whereas in the other groups bilateral sequential lung grafts were more common.

The use of perfusion fluids has changed significantly over time ($P < .001$). Use of EC solution has decreased in recent years, whereas use of LPD solution has increased in popularity (Figure 1). Similarly significant differences in individual center preferences toward a particular perfusion method were found ($P < .001$, Figure 2).

There were 70 deaths within 30 days and 166 deaths within 1 year, and 255 recipients died within 3 years of transplantation. The overall unadjusted 30-day, 1-year, and 3-year survivals for the whole cohort were 89.7% (95% CI, 87.2%–91.8%), 75.6% (95% CI, 72.1%–78.6%), and 58.1% (95% CI, 53.9%–62.1%), respectively. The median follow-up for survivors was 3 years (lower quartile, 2.1 years). Patient survival by preservation method, unadjusted for risk differences, is shown in Figure 3. Recipients of lungs perfused with BA had the lowest 3-year survival (49.3%; 95% CI, 39.4%–58.4%), whereas recipients of lungs perfused with LPD solution had the highest survival rate (62.3%; 95% CI, 51%–71.7%). The 13% survival difference across the groups was not statistically significant ($P = .72$).

Pretransplantation recipient factors included in the multivariate survival models were age group (grouped 16–40, 41–50, 51–55, and >55 years), sex, creatinine clearance, diabetes, ventilation, history of previous thoracotomy, infection, diagnosis group, and type of transplantation. Donor risk factors included were donor age group (grouped <25, 26–35, 36–50, and >50 years), sex, inotrope use, diabetes, CMV mismatch, donor-recipient size mismatch (donor body surface area <80% of recipient body surface area), blood group compatibility, organ ischemia time, and whether the organs were retrieved by the transplanting center (organ exchange). Recipient sex was included as a stratification variable because the proportional hazards assumption was not reasonable ($P = .002$ for the 30-day model). The effect of preservation method on survival was

Table 2. Pretransplantation recipient characteristics

	Euro–Collins solution (n = 284)	Blood albumin (n = 139)	Core cooling (n = 107)	Low potassium dextran solution (n = 151)	*P* value
Age (y)	51 (38–56)	53 (45–58)	51 (45–55)	50 (36–56)	.04
Female sex (n)	127 (45%)	62 (45%)	47 (44%)	64 (42%)	.9
Body mass index	22.0 (19.0–25.8)	22.3 (19.3–26.7)	22.2 (18.6–25.6)	22.0 (19.1–25.9)	.8
Diagnostic group					.014
Primary pulmonary hypertension	9 (3%)	6 (4%)	4 (4%)	2 (1%)	
Pulmonary fibrosis	88 (31%)	37 (27%)	20 (19%)	30 (20%)	
Cystic fibrosis	50 (18%)	16 (12%)	14 (13%)	42 (28%)	
Bronchiectasis	11 (4%)	6 (4%)	4 (4%)	7 (5%)	
Emphysema	113 (40%)	69 (50%)	61 (57%)	66 (44%)	
Other	13 (6%)	5 (4%)	4 (4%)	4 (3%)	
Diabetes mellitus (n)*	13 (5%)	11 (8%)	5 (5%)	14 (9%)	.2
Previous thoracotomy† (n)*	22 (8%)	21 (15%)	9 (9%)	13 (9%)	.1
Prednisolone (n)*	135 (48%)	77 (56%)	50 (49%)	54 (36%)	.008
Creatinine clearance ($mg \cdot dL^{-1} \cdot m^{-2}$)	79 (63–93)	80 (67–97)	84 (70–101)	81 (71–96)	.09
Home oxygen support (n)*	200 (71%)	103 (75%)	86 (82%)	115 (77%)	.2
Inpatient at registration (n)	34 (12%)	17 (12%)	11 (10%)	14 (9%)	.8
CMV positive (n)*	162 (59%)	79 (58%)	60 (57%)	75 (50%)	.4
Preoperative infection‡ (n)*	72 (26%)	29 (22%)	30 (28%)	51 (35%)	.1
Transplant type					
Single lung	166 (58%)	66 (48%)	47 (44%)	66 (44%)	.001
En bloc double lung	1 (<1%)	1 (<1%)	6 (6%)	3 (2%)	
Bilateral sequential lung	117 (41%)	72 (52%)	54 (50%)	54 (52%)	

CMV, Cytomegalovirus. *Less than 5% missing values. †Any operation on intrathoracic structures through a lateral thoracic incision, including operations for nonpulmonary disease, such as esophageal, cardiac, vertebral, and aortic surgery. Does not include minimal-access operations (minithoracotomy and thoracoscopic procedures), sternotomies, or mediastinotomies. ‡Microbiologically confirmed infections only. Does not include patients taking antibiotics for prophylaxis or presumed infection.

similar when adjusting for center and stratifying by center, and therefore only the stratified results are reported. For all models, the effects were consistent across the different lengths of ischemic time (ie, no interaction between perfusion method and ischemic time was indicated; $P \geq .81$). Estimated hazard ratios for perfusion technique, plus the other prespecified factors included in the model, are detailed in Tables 3 and 4, respectively. After controlling for these prespecified risk factors, perfusion technique was not identified as a significant independent predictor of recipient mortality in all 3 epochs ($P = .72$, $P = .27$, and $P = .70$ for 30-day, 30-day to 3-year, and overall 3-year survival, respectively). The proportional hazards assumption was examined for all models, and the assumption was a reasonable one for the 30-day to 3-year and overall 3-year models but was violated for the 30-day model (0.048).

Freedom from dPGD was analyzed on a subset of 631 validated records between July 1995 and December 2002. There were 302 (48%) deaths in this group, of which 108 occurred within the transplantation admission. Of these 108, 51 (47%) were validated as dPGD. dPGD were 25 (9%) in lungs preserved with EC solution, 12 (9%) in lung preserved with BA, 8 (8%) in lungs preserved with CC, and 6 (5%) in lungs preserved with LPD solution. There was no significant difference in dPGD between preservation techniques. Cumulative incidence of dPGD, as assessed by using the competing risks method, is depicted in Figure 4 and Table 5.

The median intensive care unit stay was 3 days in the EC group (interquartile range [IQR], 1–7 days), 2 in the BA group (IQR, 1–8 days), 3 in the CC group (IQR, 1–14 days), and 2 in the LPD group (IQR, 1–7 days). There was no significant difference in the median intensive care unit stay among the perfusion groups ($P = .46$), although differences across centers were found ($P < .001$). Center-specific median length of ICU stay ranged from 2 days (IQR, 1–2 days) to 7 days (IQR, 4–13 days).

The analysis of posttransplantation rejection was restricted to the subset of 629 patients undergoing transplantation after April 1996 because rejection data were not collected in the first year of the audit. Overall, 229 (36.4%) patients were free from rejection at last follow-up, and 23 had experienced more than 4 episodes of rejection in the first 3 years after transplantation (median follow-up, 2.8 years). The overall crude incidence rate was 0.72 rejection episodes per year. Rejection rates increased

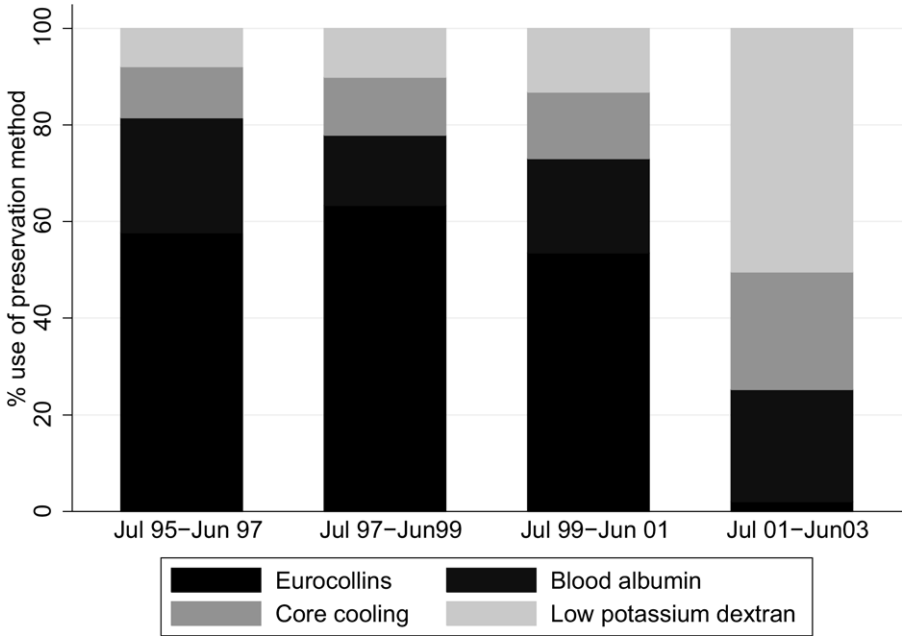

Figure 1. Use of preservation fluids over time.

with increasing ischemic time (adjusted incidence rate ratio, 1.10; 95% CI, 0.99–1.22; $P = .067$ per increase in category), and there was no evidence to suggest a differential effect with lung perfusion method ($P = .45$). Reported rejection rates have changed with time ($P = .0029$); rates were lower in the period from 1998 through 2001 than at other times. The incidence was higher among patients receiving a single lung graft compared with those receiving a bilateral graft ($P = .007$). Rejection rates varied between perfusion techniques but not consistently across centers (test for differential effect, $P = .012$). However, there was no evidence to suggest time to first rejection had changed significantly over time ($P = .39$) or that it differed with ischemic time ($P = .92$) or with lung perfusion technique ($P = .11$).

Discussion

This study suggests that currently used lung preservation techniques do not affect early or midterm survival rates, incidence

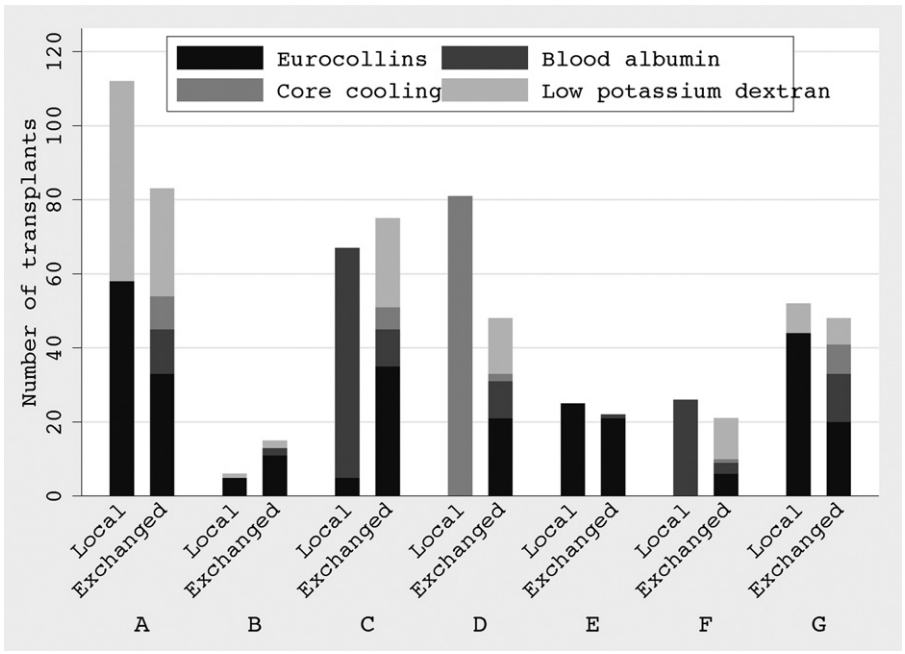

Figure 2. Use of preservation fluids by transplantation center for lungs retrieved by the transplanting center and lungs retrieved by another center (exchanged).

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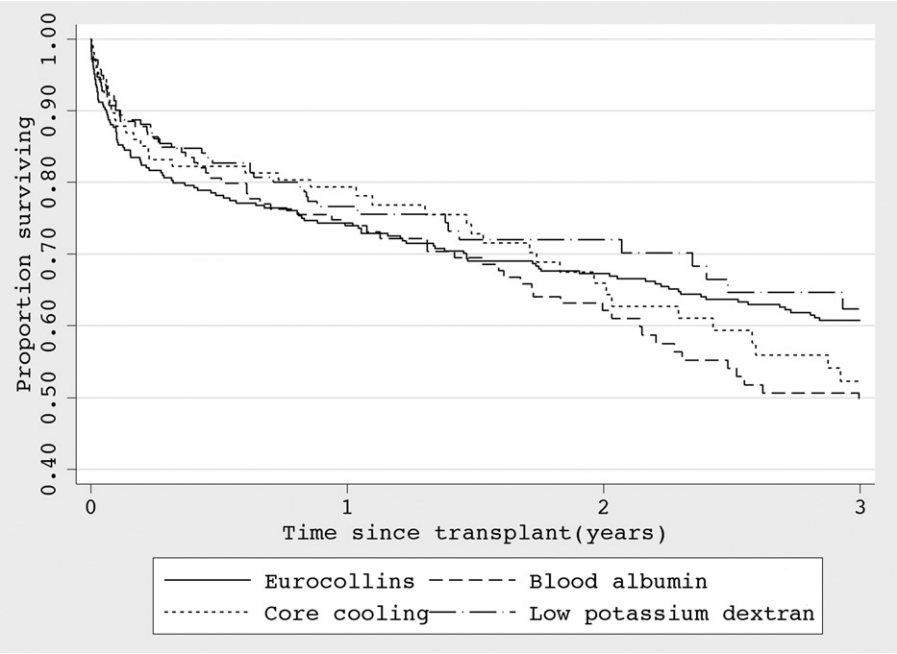

Figure 3. Patient survival by lung preservation method ($P = .7$).

of dPGD, ICU length of stay, or rejection rate. Regardless of preservation technique, rejection incidence appears to increase with ischemic time, but time to first rejection is not affected. These data are derived from a relatively large cohort of patients who underwent LTx with 4 different preservation techniques. Although modified EC solution was the main perfusate used during the study period, its dominance is being subsumed by LPD solution. In contrast to a number of previous reports that have suggested improved survival with LPD solution,[3,6,7,26,27] this has not been confirmed in a current study.[28] LPD solution is thought to be beneficial because of the low potassium concentration, which causes less endothelial injury, and the

Table 3. Recipient factors*

	Early (30-d) survival			Late (30-d to 3-y) survival			Overall (3-y) survival		
Risk factor	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age group	1.13	0.84–1.50	.42	1.12	0.93–1.34	.23	1.14	0.97–1.33	.09
Creatinine clearance	1.78	0.74–3.28	.20	1.15	0.60–2.20	.66	1.30	0.78–2.16	.31
Diabetes mellitus	2.13	0.69–6.62	.19	1.39	0.67–2.86	.37	1.58	0.87–2.90	.13
Preoperative ventilation†	5.01	0.88–28.4	.07	1.44	0.28–7.16	.66	2.33	0.73–7.42	.15
Previous thoracotomy‡	1.08	0.49–2.37	.45	1.32	0.80–2.17	.34	1.27	0.84–1.92	.20
Preoperative infection‡	1.42	0.72–2.80	.57	1.32	0.88–1.98	.14	1.31	0.92–1.84	.18
Transplant type	1.00								
Single lung	2.35	–	.57	1.00	–	.69	1.00	–	.51
En bloc double lung	1.10	0.48–11.4		1.27	0.35–4.48		1.64	0.62–4.35	
Bilateral sequential lung		0.59–2.07		0.87	0.58–1.29		0.94	0.67–1.32	
Diagnosis group									
Pulmonary fibrosis	1.00	–	<.001	1.00	–	.14	1.00	–	.007
Primary pulmonary hypertension	4.72	1.78–12.5		0.33	0.0–1.48		1.48	0.72–3.03	
Cystic fibrosis	0.20	0.06–0.68		0.79	0.37–1.66		0.56	0.30–1.04	
Bronchiectasis	0.16	0.02–1.40		0.33	0.12–0.94		0.30	0.12–0.76	
Emphysema	0.54	0.28–1.01		0.83	0.56–1.24		0.74	0.53–1.03	
Others	1.09	0.36–3.21		1.45	0.66–3.16		1.31	0.70–2.46	

CI, Confidence interval. *Stratified by transplantation center and recipient sex. †Only 5 patients were ventilated before transplantation, and information was missing on 2 patients. ‡Adjusted for missing data.

Table 4. Donor factors*

	Early (30-d) survival			Late (30-d to 3-y) survival			Overall (3-y) survival		
Risk factors	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Lung perfusion method									
Euro–Collins solution	1.00	—	.72	1.00	—	.27	1.00	—	.70
Blood albumin	0.60	0.24–1.45		1.58	0.98–2.55		1.23	0.81–1.86	
Core cooling	0.84	0.31–2.28		1.45	0.76–2.77		1.28	0.75–2.18	
Low potassium dextran solution	0.82	0.38–1.75		1.25	0.77–2.03		1.15	0.77–1.72	
Donor age group	0.90	0.70–1.15	.41	1.11	0.95–1.30	.19	1.04	0.91–1.19	.54
Female donor	0.92	0.51–1.64	.78	0.73	0.50–1.07	.11	0.85	0.62–1.16	.30
Donor inotrope use†	0.93	0.48–1.81	.12	0.71	0.48–1.06	.23	0.79	0.57–1.11	.14
Donor diabetes‡	0.89	0.10–8.04	.19	2.34	0.85–6.38	.17	1.78	0.72–4.37	.45
CMV status mismatch†‡	1.61	0.83–3.12	.13	1.57	1.06–2.34	.06	1.52	1.08–2.12	.03
Blood group variance	0.71	0.31–1.61	.42	0.84	0.54–1.31	.45	0.80	0.54–1.18	.26
Size mismatch	2.59	0.70–9.59	.15	1.78	0.56–5.60	.32	1.86	0.79–4.34	.15
Organ ischemic time									
<210 min	1.00	—	.95	1.00	—	.11	1.00	—	.30
211–270 min	1.19	0.57–2.48		1.22	0.80–1.85		1.19	0.83–1.71	
270–330 min	1.06	0.47–2.35		1.35	0.84–2.18		1.24	0.82–1.85	
>330 min	0.96	0.36–2.54		2.03	1.15–3.58		1.61	0.99–2.62	
Exchanged organ(s)	0.60	0.33–1.08	.09	0.76	0.54–1.09	.13	0.74	0.55–1.00	.05

CI, Confidence interval; *CMV*, cytomegalovirus. *Stratified by transplantation center and recipient sex. †Adjusted for missing data. ‡Cytomegalovirus-positive donor, cytomegalovirus-negative recipient.

hemorheologic properties of dextran.[28] Despite our negative finding, there was a trend toward improved longer-term survival in the LPD group and lower cumulative incidence of dPGD. It might be that the study was numerically underpowered to demonstrate a significant difference.

Thabut and colleagues[2] analyzed the effects of intracellular (EC and University of Wisconsin solution) versus extracellular (BA and Celsior) solutions and identified that extracellular preservation solutions had a lower 30-day incidence of reimplantation edema after adjusting for graft

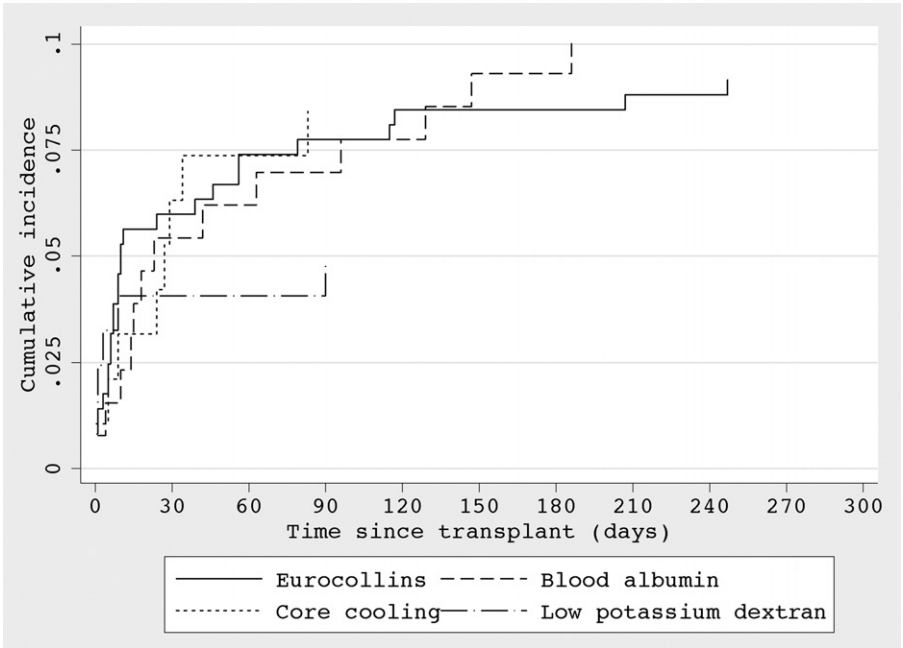

Figure 4. Deaths caused by primary graft dysfunction by lung preservation method ($P = .6$).

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Table 5. Summary of survival data by preservation technique

	30-d survival (95% CI)	1-y survival (95% CI)	3-y survival (95% CI)	Cumulative incidence of dPGD (n, last day of occurrence [95% CI])
Euro–Collins solution (n = 284)	88% (83.7%–91.3%)	74.3% (68.8%–79%)	60.7% (54.8%–66.1%)	n = 284, 247 d; 8.8% (5.9%–12.5%)
Blood albumin (n = 139)	92.1% (86.2%–95.5%)	74% (65.8%–80.5%)	49.3% (39.4%–58.4%)	n = 129, 83 d; 8.4% (3.9%–15.1%)
Core cooling (n = 107)	89.7% (82.2%–94.2%)	79.4% (70.4%–85.9%)	52.3% (40.2%–63.1%)	n = 95, 90 d; 4.9% (2.0%–9.7%)
Low potassium dextran solution (n = 151)	90.7% (84.9%–94.4%)	76.6% (69%–82.6%)	62.3% (51%–71.7%)	n = 123, 147 d; 9.3% (5.1%–15.1%)
P value	.57	.71	.72	.58

CI, Confidence interval; *dPGD*, death from primary graft dysfunction.

ischemic time. In contrast, our study did not identify any difference in survival at 30 days or 3 years among the different perfusion groups after adjusting for risk factors, including graft ischemic time. We also did not find any difference in dPGD between the extracellular and intracellular types of preservation solutions in a validated subset of recipients. This finding is confirmed by a recently published comparison of LPD and EC solution on a smaller of subset of patients, although the authors did find a lower PGD International Society for Heart and Lung Transplantation grade III incidence at T24 in the LPD group.[10]

The overall unadjusted 1- and 3-year survivals in our cohort reflect worldwide trends.[29] Recipients of lungs preserved with LPD solution had a marginally higher unadjusted survival over other recipients, but this difference was not seen after adjusting for other risk factors. Analysis of rejection episodes was restricted to a smaller subset of patients, and rejection rates increased with increasing ischemic time. We did not find any difference in rejection episodes among the perfusion groups, although we did identify a higher incidence of rejection in single-lung grafts. Whether this correlates with a decreased survival in single-lung grafts is beyond the scope of this study.

Our study has a number of limitations. Although comprising more than 600 patients, it might still be too small to demonstrate small differences in survival. Also, we could not report the full incidence or severity of PGD per se, only death attributable to PGD. However, ICU length of stay, which can be regarded as a surrogate measure of early graft function, was not different. Nevertheless, nonfatal PGD might be an important factor in determining graft longevity, and early graft dysfunction has been previously reported to be a risk factor for rejection, BOS, and late mortality.[1-3] We do not have data on reperfusion strategies, such as controlled pressure reperfusion, nitric oxide, or prostaglandin inhalation, used during the study period or whether supplemental retrograde flush perfusion was used. We have also not been able to assess the incidence or severity of BOS.

Strong center preferences for different perfusion techniques, perioperative management protocols, and differences in protocols for monitoring and identifying posttransplantation rejection that exist between centers limit the ability of the study to assess the independent effect of perfusion technique on survival, the incidence of rejection, and BOS. However, 45% of donor lungs were exchanged between centers, which reduced the confounding between centers and the preservation method. A volume-related effect was suggested for survival from 30 days to 3 years, with centers carrying out the greatest number of operations having the highest conditional survival ($P = .04$), but the effect of preservation method on survival did not vary significantly with volume ($P \geq .12$). Ischemic times are recorded consistently across centers and are not confounded with center or perfusion technique, and each center is responsible for retrieving organs from a specified region of the country and will use the organ locally where possible. Longer ischemic times are associated with greater organ injury, which appears to lead to increased incidence but not earlier rejection. Our study also has limitations in the form of absence of donor and recipient blood gas measurements. Thus, we cannot fully analyze or quantify the effect of preservation technique on early graft function. Because a temporary deterioration in gas exchange between donor and recipient is an almost constant feature of lung transplantation, the extent of this deterioration might become a useful index of preservation quality.[30]

In conclusion, in this study lung preservation technique did not affect 30-day, 1-year, or 3-year survivals; freedom from death attributable to PGD; or rejection rate. Although improved outcomes for LPD solution might become apparent in time, the case for the superiority of one technique over another remains to be proved, and it is clear that this needs to be addressed in multicenter randomized controlled trials with substantial numbers of patients using subtler end points than survival. In the absence of such trials, audits, such as the UKCTA, require more detailed data accrual of pretransplantation and posttransplantation donor lung function, together with robust criteria to determine the incidence and severity of PGD.[31] Such audit data are likely to improve our understanding of the effect of different preservation and reperfusion techniques on lung transplantation outcomes.

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We thank the Unit Data Coordinators, Sharon Beer, Heather Constance, Yvonne Davenport, Joanne Hasan, Myra Kerr, Vince Salter, Kirsty White, and Pauline Whitmore. We are also indebted to the Data Executive at UK Transplant who initially accrued and assimilated the data for analysis by the UKCTA.

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